Amendments to the Specification

On page 1, please replace the paragraph starting on line 15 with the following:

This invention relates generally to a method for performing tissue characterization using minimally invasive methods. More particularly, the invention relates to a method and apparatus for performing an in vivo tissue characterization to identify and discriminate between diseased and healthy tissue using localized measurement of tissue impedance. Still more particularly, the invention to relates to a method and apparatus for performing tissue characterization before during and after ablative therapy using localized complex impedance measurement to monitor and titrate the delivery of ablative therapy to improve clinical outcomes.

On page 2, please replace the paragraph starting on line 30 with the following:

The apparatus can be configured to detect, locate and identify tumorous tissue at a selected tissue site using impedance measurements such as multi-pathway measured impedance, complex impedance and impedance vector measurements. For complex impedance real and imaginary components of the impedance signal can be used to determine more refined bioelectric parameters such as interstitial and intracellular impedance and cell membrane capacitance that provide greater sensitivity and predictive power of cell necrosis or malignancy. Also, the apparatus can ~~also~~ be configured to utilize one or more impedance measurements to monitor a target tissue site and control the course of ablative therapy before during or after the delivery of ablative energy or other treatment to the tissue site. Accordingly the apparatus can be configured to be used independently or in conjunction with another ablative apparatus such as an RF, microwave or laser ablation apparatus. Further, the apparatus can be configured to utilize multi-path impedance measurement to monitor two or more tissue volumes including a tumor volume, a developing ablation volume and an adjacent anatomical structure. Additional embodiments of the apparatus can also be configured to utilize impedance measurements such as complex, vector or locus impedance measurements to generate an image of a target tissue site and display the image to facilitate the location and monitoring of a tumor and/or ablation volume.

On page 3, please replace the paragraph starting on line 19 with the following:

In the use, the apparatus would be positioned at a selected tissue site previously imaged and found to contain a tumor or other tissue mass. The apparatus would be introduced and positioned at the tissue site using the elongated delivery device or an introducing device known in the art. The impedance array would then be deployed and used to measure impedance including complex impedance and capacitance through one or more conductive pathways. This information could be analyzed by coupled logic resources and then utilized to locate the position of and borders of the tumor volume and/or identify the tumor or tissue type. Also, the information could be processed by the logic resources or other processing means to generate an image of the tissue site including the tumor volume which could utilize the locus of impedance as a way to indicate the center of the tumor mass or otherwise visually enhance the detection and display of the tumor mass. This information could then be used to position the energy delivery device to produce the desired ablation volume. Once the energy delivery device was positioned, the impedance array could then be utilized to monitor and/or control the delivery of ablative energy or therapy to the tumor volume including monitoring the size and shape of a developing ablation volume in relation to size and location of the tumor volume. This allows the medical practitioner to not only determine the degree to which the tumor volume has been ablated, but also allows for the control of the amount of healthy tissue margin around the tumor volume one or all of which allow for the determination of a desired clinical endpoint. Further, it allows the practitioner to titrate or otherwise control the delivery of energy or other ablative therapy to control rate of growth of the ablation volume (and in turn the overall ablation time) as well as the final shape and size of the tumor volume. Multiple tissue volumes can be simultaneously monitored and compared to monitor progress of the ablation volume, assure uniform ablation or necrosis throughout the tumor or ablation volume and provide real time assurance that surrounding healthy tissues and structure were not injured. For example, tissue volume at the center, and one or more peripheries of the tumor mass could be simultaneously or near simultaneously monitored to assure uniform necrosis at all locations and hence throughout the tumor volume. Impedance measurements can be taken simultaneously or sequentially at

multiple conductive pathways passing through the target volume (at convergent divergent and paths) to provide a higher confidence of uniform ablation by reducing the size of un-sampled zones within the target volume as well any directional bias of the measurements. The multiple conductive pathways can be selected electronically via a controllable switching device or manually by rotational, lateral or longitudinal movement of the impedance array within the target volume. In the former case, the user could program the conductive pathways via a coupled monitoring device and in the latter, the user could rotate, advance, retract or deflect the impedance array via the elongated delivery device or via a deployment, advancement or deflection device mechanically coupled to the impedance array or delivery device. In addition to real time impedance measurement during the ablation process, measurements can also be taken post ablation at one or more pathways, (including pathways different than those used during inter-ablative monitoring) and compared to baseline measurements or an impedance database to provide a further indication of a complete ablation and/or clinical endpoint. Endpoints can also be determined based on ratios of intracellular to interstitial impedance as well as a characteristic shape of the impedance or complex impedance curve including determinations of thresholds, slopes or inflection points.

On page 6, please replace the paragraph starting on line 15 with the following:

Figure 6 is a perspective view illustrating an embodiment of an apparatus for detecting and treating tumors including an impedance monitoring having memory resources and logic resources including software modules to analyze impedance data and generate impedance profiles and images.

On page 10, please replace the paragraph starting on line 7 with the following:

A discussion will now be presented of impedance measurement theory and impedance measurement methods employed by embodiments of the invention. In order to measure ~~in~~ tissue impedance or impedivity (which typically has units of impedance/cc of tissue at 20°C.) a current is applied across the tissue and the resulting voltages are measured. This current, known as the excitation current or excitation signal is relatively

small in comparison to an ablative RF or other ablative current and hence results in no appreciable ablative effect. In various embodiments the excitation current can range from 0.01 ma to 100 amps with specific embodiments of 0.1, 1.0 and 10 amps which can be delivered in a continuous or pulsed fashion using a duty cycle. In various embodiments, the duty cycle can be in the range of 5 to 50% with a pulse duration of 10 to 200 ms. The average power delivered over the course of the duty can be in the range of 0.1 to 10 watts. In these and related embodiments the excitation current source is used to measure voltage differences between two or more selected impedance sensors/sensing member in a bipolar mode or one or more sensors/sensor members and a common ground. The known excitation current and measured voltage are then used to derive impedance using algorithms and methods described herein and/or known in the art.

On page 11, please replace the paragraph starting on line 20 with the following:

Complex impedance includes both real and imaginary components, which reflect the phase shift between voltage and current (*e.g.* the voltage can lead or lag current depending on the electrical properties of the tissue). Various embodiments of the invention can be configured to record ~~and~~ both the real and imaginary components of complex impedance. This provides the benefit of providing more comprehensive information on the tissue allowing analysis with a greater degree of accuracy, precision and resolution. These components can be determined by passing an excitation current through the target tissue and measuring impedance and/or any phase shift between the current and voltage as the signal is conducted through the target tissue.

On page 12, please replace the paragraph starting on line 10 with the following:

In specific embodiments, the three parameters can be used to detect various physiologic indicators of ablation and cell necrosis including cell lysis, cell membrane swelling (indicated by an increase in membrane capacitance), cell membrane rupture (indicated by a sharp decrease in membrane capacitance), a decrease in extracellular fluid (indicated by an increase in intracellular impedance) and in increase in intracellular fluid (indicated by a decrease in extracellular fluid). Other parameters which can be calculated

and used for detection and control purposes include the absolute value of the impedance or admittance, the phase of the impedance (*e.g.* the phase difference between the current and the voltage), the capacitance or a function of a combination of the impedance and admittance components.

On page 20, please replace the paragraph starting on line 27 with the following:

In various embodiments apparatus 10 can be configured to simultaneously sample different locations within target tissue site 5' utilizing switching device or multiplexer 29 or other switching means described herein or known in the art. In an embodiment shown in Figure 5 a first group of selected conductive pathways 22cp' can be used to sample a local first volume 5sv1 and a second group of selected conductive pathways 22cp'' can be selected to do so for a second volume 5sv2 and a third group of selected conductive pathways 22cp'; can be so selected to do so for a larger or global sample volume 5sv3 defined or circumscribed by multiple sensor tipped members 18 or sensing members 22m. Each sample volume results in a separate impedance profile 19p. Thus sample volumes 5sv1, 5sv2 and 5sv3 produce impedance profiles 19p1, 19p2 and 19p3 respectively, all or portion of which can be compared to one another or a database of impedance profiles 19db using comparison/pattern recognition algorithms of module 19m other software or computational means. In a related embodiment the measured impedance signal for each sample volume can be integrated or otherwise analyzed by module 19m or other computational means to determine an impedance vector 22v and loci of impedance 22i for each respective sample volume (*e.g.* impedance vectors 22v1, 22v2, 22v3; and impedance loci 22l1, 22l2 and 22l3).

On page 22, please replace the paragraph starting on line 21 with the following:

In various embodiments, apparatus 10 along with impedance monitoring device 19 can be configured to perform tissue identification, differentiation, ablation monitoring and mapping of tissue masses and structures. In specific embodiments, monitoring device 19 is configured to perform a tissue identification function using impedance information derived from sensors 22, sensing members 22m or array 22a. A discussion will now be

presented on the background of tissue monitoring and identification using impedance measurement. Owing to variations in composition and morphology various tissue types have different electrical properties (*e.g.* conductance, inductance, capacitance *etc.*) and therefore conduct electrical energy differently particularly at certain frequencies. For example, cancerous tissue will typically have a significantly higher phase than the health tissue, particularly at low frequencies. These differences in electrical properties, particular conductance result, in a characteristic impedance profile 19p for a given tissue type or condition when the tissue is exposed to an excitation current at one or more specific frequencies. Impedance profile 19p can have one or more peaks 19pk, curves and other shapes that serve as a fingerprint of the tissue type or tissue condition. Accordingly by analyzing the impedance profile 19p and matching peaks, curve shapes, thresholds etc, profile 19p can be utilized by embodiments of the invention to identify tissue types and conditions such as malignancy, vascularity, necrosis, thermal injury *etc.* Related conditions that can also be identified using this approach include abnormally mutated tissue, abnormally dividing tissue or hypoxic tissue.

On page 29, please replace the paragraph starting on line 24 with the following:

As described herein, in various embodiments all or a portion of resilient member 18 can be an energy delivery device or member 18e. Turning to a discussion of energy delivery device and power sources, the specific energy delivery devices 18e and power sources 20 that can be employed in one or more embodiments of the invention include but are not limited to, the following: (i) a microwave power source coupled to a microwave antenna providing microwave energy in the frequency range from about 915 MHz to about 2.45 GHz (ii) a radio-frequency (RF) power source coupled to an RF electrode, (iii) a coherent light source coupled to an optical fiber or light pipe, (iv) an incoherent light source coupled to an optical fiber, (v) a heated fluid coupled to a catheter with a closed or at least partially open lumen configured to receive the heated fluid, (vi) a cooled fluid coupled to a catheter with a closed or at least partially open lumen configured to receive the cooled fluid (viii) a cryogenic fluid, (ix) a resistive heating source coupled to a conductive wire, (x) an ultrasound power source coupled to an ultrasound emitter, wherein the ultrasound power

source produces ultrasound energy in the range of about 300 KHZ to about 3 GHz, (xi) and combinations thereof. For ease of discussion for the remainder of this application, the energy delivery device 18e is one or more RF electrodes 18e and the power source utilized is an RF power supply. For these and related embodiments, RF power 20 supply can be configured to deliver 5 to 200 watts, preferably 5 to 100, and still more preferably 5 to 50 watts of electromagnetic energy ~~is~~ to the electrodes of energy delivery device 18 without impeding out. The electrodes 18e are electro magnetically coupled to energy source 20. The coupling can be direct from energy source 20 to each electrode 18e respectively, or indirect by using a collet, sleeve and the like which couples one or more electrodes to energy source 20.

On page 30, please replace the paragraph starting on line 19 with the following:

In various embodiments, electrodes 18e ~~including~~include impedance sensors 22 and sensing members 22m can have a variety of shapes and geometries. Referring now to Figures 15a-15f, example shapes and geometries can include, but are not limited to, ring-like, ball, hemispherical, cylindrical, conical, needle-like and combinations thereof. Referring to Figure 16, in an embodiment electrode 18e can be a needle with sufficient sharpness to penetrate tissue including fibrous tissue including, encapsulated tumors cartilage and bone. The distal end 18de of electrode 18e can have a cut angle 68 that ranges from 1 to 60°, with preferred ranges of at least 25° or, at least 30° and specific embodiment of 25° and 30°. The surface of electrode 18e can be smooth or textured and concave or convex. Electrode 18e can have different lengths 38 that are advanced from distal end 16' of introducer 12. The lengths can be determined by the actual physical length of electrode(s) 18e, the length 38' of an energy delivery surface 18eds of electrode 18e and the length, 38'' of electrode 18e that is covered by an insulator 36. Suitable lengths 38 include but are not limited to a range from 1-30 cms with specific embodiments of 0.5, 1, 3, 5, 10, 15 and 25.0 cm. The conductive surface area 18eds of electrode 18e can range from 0.05 mm2 to 100 cm2. The actual lengths of electrode 18e depend on the location of tissue site 5' to be ablated, its distance from the site, its accessibility as well as

whether or not the physician performs an endoscopic or surgical procedure. While the conductive surface area 18eds depends on the desired ablation volume 5av to be created.

On page 32, please replace the paragraph starting on line 10 with the following:

Referring now to Figures 17 and 18, electrode 18e can also be configured to be flexible and or deflectable having one or more radii of curvature 70 which can exceed 180° of curvature. In use, electrode 18e can be positioned to heat, necrose or ablate any selected target tissue volume 5'. A radiopaque marker 11 can be coated on electrodes 18e for visualization purposes. Electrode 18e can be coupled to introducer 12 and or an advancement member or device 15 or ~~and~~ advancement-retraction member 34 using soldering, brazing, welding, crimping, adhesive bonding and other joining methods known in the medical device arts. Also, electrode 18e can include one or more coupled sensors 22 to measure temperature and impedance (both of the electrode and surrounding tissue), voltage and current other physical properties of the electrode and adjacent tissue. Sensors 22 can be at exterior surfaces of electrodes 18e at their distal ends or intermediate sections.

On page 35, please replace the paragraph starting on line 1 with the following:

Turning now to a discussion of impedance sensors, in various embodiments impedance sensor 22 can include all or a portion of resilient members 18. Referring back to Figure 19, when resilient member 18 is made of a conductive material the length 22l of impedance sensor 22 can be defined by the placement of a slidable or fixed insulative layer 36. Also in various embodiments impedance sensors 22 can fabricated from a variety of conductive materials and metals known in the art including stainless steel, copper, silver, gold, platinum and alloys and combinations thereof. Referring now to Figure 24, similarly all or portions of sensors 22 or sensor members 22m can comprise a conductive coating 22c that is coated or deposited onto a selected portion of member 18 using. In various embodiments, coating 22c can comprise a conductive metal or conductive polymer coating known in the art that is applied using known methods such as sputtering, vacuum deposition, dip coating, photolithography and the like. In a related

embodiments, impedance sensing members 22m and/or sensor 22 can be configured to have a resistance gradient 22g along all or portions of their lengths 22l. The resistance gradient can be increasing or decreasing in a linear, second order, third order, exponential or other fashion. In a specific embodiment the resistance gradient is configured to compensate for resistance losses (i.e. of voltage) and/or hysteresis occurring along the length 22l of member 22m or sensor 22, as well as changes in the overall resistance of sensor 22 due to changes in the temperature and/or conducting/sensing length 22lc (and area) of sensor 22 as might occur due to advancement or retraction of slidable insulation layer, or ~~fowling~~fouling of the sensor with, desiccated, burnt tissue or otherwise adherent tissue. In this and related embodiments the gradient can be so configured to produce the least resistance (e.g. maximum conductance) at the distal tip 22d of the sensor 22 and increasing moving in a proximal direction along. The gradient can be produced via the use of coating 22c either by varying the thickness or composition of the coating, or a combination of both along the length 22l of the sensor using methods known in the art. Further, by compensating for such resistance changes or losses along the length or area of impedance sensor 22, these and related embodiments also improve the measurement and detection of real and imaginary components of complex impedance. In other related embodiments, the resistance gradient can be in a radial direction or a combination of radial and linear directions with respect to the sensor length 22l.

On page 36, please replace the paragraph starting on line 13 with the following:

In an embodiment, sensor 22 can be selected to measure temperature along with impedance to compensate for any temperature related bias or hysteresis in the impedance measurement. Accordingly, in an embodiment a feedback signal from a temperature sensor or temperature calculation device 342 can be input~~ted~~ to the impedance calculation device 334 described herein to compensate for such variation. Temperature monitoring can also be used to perform real time monitoring of ablative energy delivery. If at any time sensor 22 determines that a desired cell necrosis temperature is exceeded, then an appropriate signal can be sent to power control circuitry describe herein to reduce or regulate the amount of electromagnetic energy delivered to electrodes 18 and 18'.